NATIONAL INSTITUTE FOR MATERIALS SCIENCE
NIMS NOW INTERNATIONAL
No.3
2015

New age of medical materials

Nano-Biomaterials Research to Save Lives

We still can do a lot in research to save lives and cure physical problems.

Nano-biomaterials, New age of biomedical materials

It is vital for medical and engineering scientists to work together in efforts to pioneer innovative biomedical technologies. Through the fusion of nanotechnology with medical and biological knowledge and techniques, medical treatment is progressing rapidly. NIMS's Tissue Regeneration Materials Unit and Biomaterials Unit regularly engage in R&D on drug delivery systems and materials for regenerative medicine. They are working to realize a system by which everyone can easily receive medical treatment, while striving to understand the potentials of the medical materials. To save lives and cure physical problems——that is the vision they share.

The Path to Success of Biomaterials Science

Missions to be fulfilled by NIMS

Biomaterials for the advancement of medicine

As the practical application of regenerative medicine, artificial organs, drug delivery systems (DDS) and biochips is being realized, it is anticipated that the importance of biomaterials science will increase more and more. We invited three leading researchers in this field to discuss the past, present and future of biomaterials science and the role NIMS should play in this field.

Yukio Nagasaki
Professor, Graduate School of Pure and Applied Sciences, University of Tsukuba

Toshihiro Akaike
Director, Biomaterials Center for Regenerative Medical Engineering Foundation for Advancement of International Science(Professor Emeritus, Tokyo Institute of Technology)

Guoping Chen
Field Coordinator, PI and Unit Director of the Tissue Regeneration Materials Unit and Biomaterials Unit, Nano-Bio Field, International Center for Materials Nanoarchitectonics (MANA), NIMS

The Path to Success of Biomaterials Science

Missions to be fulfilled by NIMS

History of biomaterials science

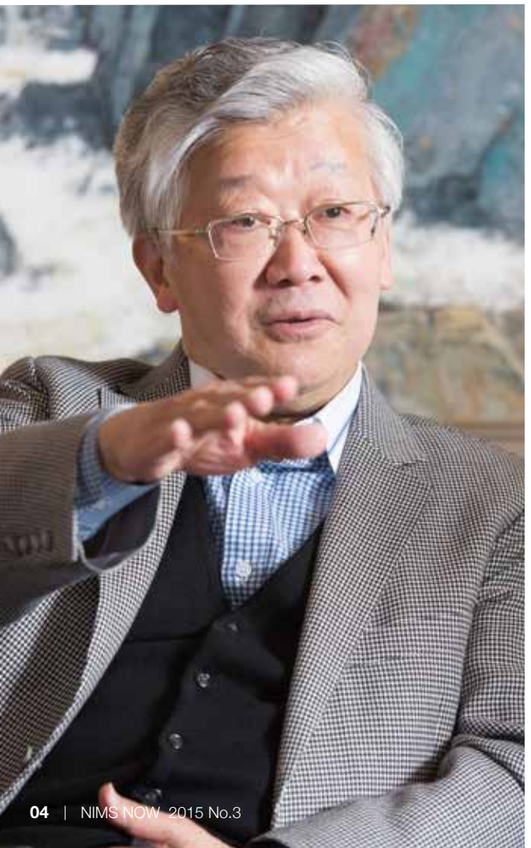
Chen: Professor Akaike, you have said that biomaterials science has passed through its first and second phases and is now entering the third phase. You are one of the leading scientists in this field with about 40 years of experience. Could you tell us what you see when you look back on the history of the field?

Akaike: Let me start from the very beginning which we call the first phase. In Japan, biomaterials science was first practiced in the 1960s in the context of research and development of artificial organs. The early R&D of artificial hearts, lungs and kidneys was led by surgeons at the University of Tokyo including Professor Kazuhiko Atsumi, who is known to have served as a model for Professor Ochanomizu, a famous character in animation "Astro Boy," and his junior late Professor Yasuhisa Sakurai.

Later, in 1975, Professor Teiji Tsuruta encouraged me to participate in the biomaterials research launched at Professor Sakurai's lab in Tokyo Women's Medical University. Thus, I became the first polymer materials engineer on the official medical staff there. Since then, many other young and energetic engineers joined the program including Professor Teruo Okano at Tokyo Women's Medical University, who is famous for regenerative medicine using cell sheets, and Professor Kazunori Kataoka at the University of Tokyo, who is famous for his research on polymeric micelles that are used in DDS to deliver drugs to the affected part of the body. This is the beginning of the second phase of biomaterials research.

NIMS should stand as a new leader in the biomaterials frontier

Toshihiro Akaike



Nagasaki: I heard that Professor Kataoka, who was fascinated by Professor Tsuruta's lectures when he was a student at the University of Tokyo, joined Tsuruta's lab where he studied polymeric micelles. As a matter of fact, I myself was captivated by the lectures of Professor Tsuruta as he became a professor at Tokyo University of Science during my junior year there, and decided to seek a career in polymer chemistry.

Akaike: As you just illustrated, the students who were influenced by the first-phase leaders took initiatives in the second and third phases. The second phase was led by such universities as the University of Tokyo, Tokyo Women's Medical University and Waseda University. In western Japan, such professors as Seizo Okamura (deceased), Akio Nakajima (deceased), Yukio Imanishi, and Yoshito Ikada, all of who were taught by late Professor Ichiro Sakurada, considered to be one of the fathers of polymer science research, founded the Medical Polymer Research Center on the campus of Kyoto University in 1980. In addition, people such as Professors Hiroo Iwata and Yasuhiko Tabata who are still active in research today, and Professor Yoshihiro Ito who is currently the chief scientist at RIKEN, were practically leading Kyoto University's biomaterials research group at that time.

Chen: Professors Imanishi and Ito were my supervisors when I was at Kyoto University. I guess I am eligible to be added to the lineage of these great researchers.

Akaike: Certainly. Now, unlike the first phase during which medical doctors led the research, in the second phase, R&D on polymeric biomaterials was carried out from the perspective of engineers using more scientific approach. We worked in the new research field that resulted from the fusion of medicine and engineering, with a sense of excitement and with dreams and hopes. I felt the experience was metaphorically comparable to the eve of the revolution. Late Professor Sakurai named this new discipline "Materials Biochemistry." Today, it is called "Biomaterials Science."

Nagasaki: The focus of the second phase was to search for materials suitable for the creation of high-performance biomaterials. Many materials were tested or developed during this stage. Outstanding examples among them are biocompatible polymers such as poly(ethylene glycol). Also, polymeric micelles that Professor Kataoka has studied and developed over many years will finally be put to practical use next year. Poly(2-methacryloyl oxyethyl phosphorylcholine) (MPC) has been also developed by Professor Ishihara, spending a long time. As this illustrates, biomaterials are gradually optimized through decades of trial and error, and their practical applications are achieved at the end. Development of biomaterials typically takes longer than studies of other types of materials.

Beginning of the third phase

Akaike: Entering the 1990s, biomaterials research adopted molecular biology, cell biology and regenerative medicine that had advanced rapidly. This is the beginning of the third phase. Research was carried out with the aim of developing biomaterials for artificial organs by analyzing and controlling materials' biocompatibility with tissues and organs at the gene level. This emerging area of research is called "materials genomics."

I briefly described the evolution of biomaterials science up to the beginning of the third phase. Both of you, Dr. Nagasaki and Dr. Chen, made great contributions during the second phase and are expected to continue doing so in the third phase.

Nagasaki: My research was not specialized in biomaterials in the beginning. Instead, I was studying polymer synthesis at that time. Specifically, I was developing a methodology of new polymer synthesis and applied them for functional polymers such as gas separation membranes. After Professor Kataoka moved to Science University of Tokyo, I learned a lot from him about the importance of biomaterials and how to apply materials for these objectives. For example, the oxygen permselective membrane which we have designed and synthesized was applicable for artificial lungs and so on. After that, I shifted my research focus to biomaterials as that field was enjoyable and fulfilling.

At present, I am engaging primarily in R&D of biomaterials capable of removing oxidative stress that may contribute to cancers, aging and strokes, etc. In addition to their anti-aging effect, biomaterials have a wide range of applicability such as in radiation damage and environmental fields, and thus are promising materials.

Chen: Ever since I was a student, I have been carrying out research with two focuses: elucidation of mechanisms involved in the interaction between biomaterials and cells, and preparation of scaffolds for regenerative medicine. This is because it is essential to reveal the interactions occurring at the interfaces between cells and scaffolds in order to develop ideal scaffolds for cell proliferation and tissue regeneration.

Perhaps it is easier to understand regenerative medicine if I use rice farming as a metaphorical example. Let's assume that cells are rice seeds, a scaffold is a rice field and cell growth factors are fertilizer. Even if there are abundant rice seeds, rice cannot be grown unless there is a rice field. Likewise, regeneration of large tissues with complex structures is impossible without scaffolds. By elucidating the cell-material interactions and preparing highly functional and biocompatible scaffolds, I would like to make my best contribution for the advancement of regenerative medicine.

NIMS's active engagement in medicine-engineering collaboration

Akaike: Professor Nagasaki, you said earlier that it takes a long time to develop biomaterials. I totally agree with you. I myself turned my attention to the sophisticated in-vivo mechanism, such as antibodies and enzymes, to recognize cells, and have been working on the development of cell-recognizing and function-controlling biomaterials since 1986. Only recently, after 30 years of study, have I realized that practical application of the material is feasible. I presume that a major turning point is coming in the near future in terms of the practical application of biomaterials science.

On the other hand, in the area of regenerative medicine Dr. Chen has been working on, it seems that the fusion between medicine and engineering, especially chemical engineering, has been progressing very slowly. What is the actual situation in that regard? I am hoping to see rapid advancement of biomaterials science during the third phase through fusion between the two fields.

Chen: NIMS researchers not only create new biomaterials and scaffolds, but also are very active in promoting medicine-engineering collaboration given that more than 20 such collaborative projects are underway. In particular, we are working very closely with some medical doctors at Faculty of Medicine, University of Tsukuba by periodically holding tours to observe real surgery in action and lectures by clinicians. Through these activities, the two parties are striving to build mutual understanding and good collaborative relationship.

It is extremely vital for us to understand the exact needs at medical sites by listening to the opinions of on-site medical workers. We believe that the most logical and efficient approach for us to take is to identify the needs of clinical sites first and then carry out studies accordingly, rather than starting with basic research and applying the outcome to clinical needs. In this view, collaboration between medical and engineering experts is essential and it needs to be further strengthened.

Nagasaki: The common problem of collaboration in medical field is that communication is often difficult between the two parties due to the different languages they use. I urge young engineering researchers to make steady efforts in understanding medical language. Moreover, medical doctors have focused on specific field such as the lungs or heart. I recommend persons for engineering side make acquaintance with many medical doctors with different field and also a person who has wide variety of knowledge like anesthesiologists. I think such a flexible collaboration approach based on various perspectives is necessary for truly successful material development.

"It is vital to foster researchers in this field."

Yukio Nagasaki

NIMS has adequate resources to tackle challenging projects

Chen: In regard to R&D of biomaterials, NIMS has researchers with expertise in inorganic materials, metals, polymers and biology, and they work closely with each other. NIMS is quite unique for its capability to handle such a broad range of materials.

We attempt to disclose the effect of biomaterials on cells at various scales such as nano- and micro-levels. For example, to optimize interactions between metals and living cells, it is necessary to modify the surfaces of the metals. And to achieve the modification, knowledge and techniques related to polymeric materials are indispensable. From this perspective, I am confident that NIMS offers the best environment for such types of study.

Akaike: As NIMS is a world-class materials research organization, I earnestly hope that it will yield good results in the field of biomaterials by setting sound plans, taking advantage

of its strong organizational framework and upholding a firm sense of mission.

At the same time, there are many issues concerning biomaterials studies today. Professor Nagasaki, what are your thoughts on that?

Nagasaki: My major concern is that there are not enough researchers in this field despite the fact that there are so many research subjects to be worked on. While many students are interested in this field, biomaterials research also requires funding, experimental animals, various instruments and a certain amount of space. These requirements are acting as a high hurdle for young researchers.

I feel that NIMS is capable of playing a major role in this regard. It is equipped with cutting-edge equipment such as analysis devices and electron microscopes, and has sufficient space. Furthermore, NIMS researchers have expertise in many types of materials, so young researchers can ask for their advice or support as needed. I believe that NIMS can provide an adequate research environment, encouraging young researchers to tackle biomaterials studies that would otherwise be extremely difficult to perform on their own. I hope that NIMS, and especially its component MANA (International Center for Materials Nanoarchitectonics), one of the WPI (World Premier International Research Center Initiative) program, will attract many young and talented researchers not only in Japan but also overseas.

Akaike: Since practical application of regenerative medicine and DDS are expected to advance rapidly in the future, I am sure that demands for biomaterials scientists will increase. This growing field is very promising and highly anticipated.

"Biomaterials will realize humankind dream to be healthy forever.."

Guoping Chen

Nagasaki: That trend is clear based also on the fact that the pharmaceutical industry is beginning to hire more people having experience in polymer chemistry and biomaterials. In addition, film and fiber manufacturers also have started advancing into this field.

Most of universities in the United States newly opened a bioengineering department. This is a sign that employment demand in this field will increase in the future. So, I hope that the Japanese government will also recognize the importance of training researchers in this field (We have only limited universities opened bioengineering school).

Chen: My impression is that the number of biomaterials researchers is increasing slowly but surely. I assume that most people desire to stay young and healthy as long as possible. Biomaterials are the key to make that dream come true. Long time ago, research had been conducted aiming to obtain eternal youth and immortality. While that goal may be unrealistic, biomaterials have the appeal of perhaps realizing such everlasting dream of humankind. Biomaterials research requires a certain degree of perseverance and patience, but I would enthusiastically encourage young researchers to take up the challenge.

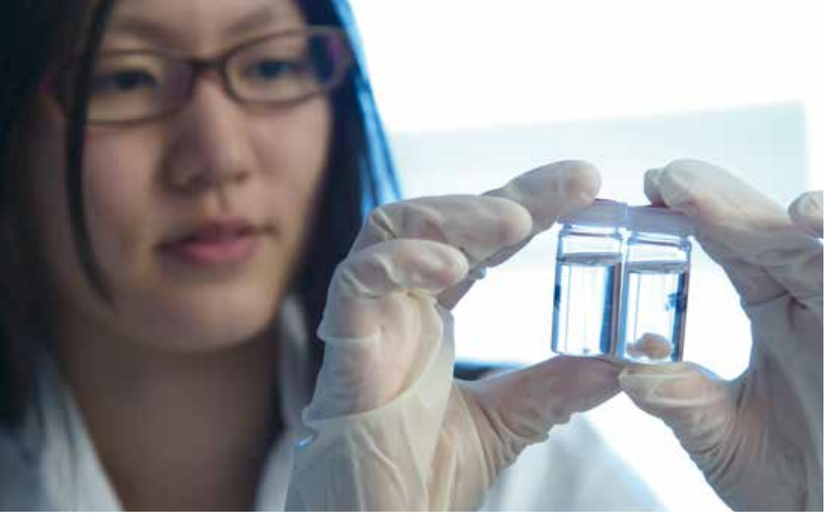
Nagasaki: As the fusion of biomaterials science with other disciplines progressed through the first, second and third phases, the interdisciplinary nature greatly expanded, making it difficult for students to fully learn and understand it. I think that is one reason for the existence of the high hurdle that is discouraging young researchers from participating in biomaterials science. On the other hand, quite a few young researchers studying inorganic materials and metal materials are interested in studying biomaterials. I would like to see pioneers of biomaterials science such as Dr. Akaike support the education of prospective researchers by holding seminars for them. What do you think about this idea?

Akaike: Somebody has to commit to recreating the lively research environment that existed during the second phase, where researchers can have dreams and hopes. I will, of course, do my part. I would also like to see NIMS fulfill its role and launch a framework that will facilitate the advancement of biomaterials research. That is my bottom line message to NIMS.

Chen: On behalf of the researchers of biomaterials science in NIMS, I will seriously take the advice given by both of you, forerunners of biomaterials science, and take proper actions. Thank you for your time today.

Nanofiber to fight against cancer

Nanofiber sheets, a material that Mitsuhiro Ebara at NIMS has been developing, can be used to apply thermotherapy and chemotherapy at the same time by attaching them directly to cancer cells in the body. Ebara says that the material exhibits outstanding therapeutic effect, and that he is fortunate to have worked with very talented people in this project. One of such examples is the collaboration with Associate Professor Chun Man Lee, who is also a medical doctor, at the Department of Medical Innovation, Osaka University Hospital. We asked Ebara about the current status of progress in achieving the practical use of nanofiber sheets.



Samples of cancer in mice. There is a visible difference between the left bottle in which a sheet is attached and the right bottle in which no sheet was used. You can see that the cancer to which a sheet is attached is almost completely dead. The person holding the sample is Eri Niiyama, a first-year master's student at the University of Tsukuba and a member of Ebara's research team.

Mitsuhiro Ebara
MANA scientist, Smart Biomaterials Group, Biomaterials Unit

Chun Man Lee
Board Certified Surgeon by JSS & General Clinical Oncologist by JBCT, Associate Professor, Department of Medical Innovation, Osaka University Hospital

Cancer has been the No. 1 cause of death in Japan since 1981. Today, more than 300,000 Japanese people die of cancer every year. Globally, the number of cancer patients is estimated to increase by more than 75% from the current level by 2030. Some members of Ebara's research team have also lost their family members to cancer. So this disease is a serious concern to many of us.

In 2013, Ebara published a study on a new material highly effective in cancer treatment called a nanofiber sheet that is used to apply "chemotherapy" with anticancer drugs and "thermotherapy" with heat at the same time. It has been known that the effect of anticancer drugs used in chemotherapy will be improved by simultaneous application of thermotherapy by which cancer cells are heated and weakened. However, synchronized application of the two kinds of therapies targeting the same location in a controlled manner was thought to be technically difficult. When directly attached to cancer cells, the nanofiber sheets Ebara is developing release anticancer drugs while heating the cells at the same time, effectively killing cancer cells. With the goal of achieving practical use of the nanofiber sheets, Ebara is carrying out joint research with Chun Man Lee, Associate Professor, Department of Medical Innovation, Osaka University Hospital, and has been performing animal experimenting once a month at most.

Simultaneously manipulating "chemotherapy" and "thermotherapy"

A nanofiber sheet is a nonwoven fabric consisting of nanofibers of about 500 nanometers in diameter. It looks like an ordinary thin fabric, but in fact each fiber contains anticancer drugs and magnetic particles.

The mechanism involved in the destruction of cancer cells is as follows. First, an alternating magnetic field is applied from the outside to the magnetic particles. This causes the magnetic particles to generate heat in a manner similar to how an IH heater generates heat. The heat suppresses the activity of cancer cells as they are more susceptible to heat than are normal cells. The heat also shrinks nanofibers and make the anticancer drugs inside them to seep out and attack cancer cells. This two-step attack works in great synergy compared to the application of heat or anticancer drugs alone.

"I treated mice with cancer (using the nanofiber sheet) for 15 minutes at a time, once a week during a two-month study period. While cancer in the untreated mouse group grew more than 10 times its original size, cancer in the treated mouse group grew smaller than one-fifth of its original size. The results were more dramatic than I expected," says Ebara.

Before conducting animal testing, Ebara had confirmed the effect of the nanofiber sheets in lab experiments using cancer cells cultured in petri dishes. At that time, he gained substantial confidence in this technology. However, the great effectiveness observed in the mouse study was beyond his expectations.

It is not difficult to manufacture this highly effective material. First, dissolve polymers, whose molecular structures change greatly with temperature, a crosslinking agent that joins polymers, anticancer drugs and magnetic particles in an organic solvent. When the solution is sprayed from a nozzle while being applied with high voltage, it turns into nanofibers. Then by simply laminating the nanofibers, a nanofiber sheet can be created. However, its function is controlled at the nanometer scale.

When polymers are cross-linked, anticancer drugs and magnetic particles become confined in the nanofibers. The anticancer drugs, made of small particles, can seep out through gaps in the nanofibers whereas the larger magnetic particles cannot.

The nanofibers are designed to shrink at a temperature of about 43°C. This is the precise temperature at which cancer cells start weakening while normal cells are unaffected. When the temperature rises above 45°C, normal cells are also damaged. "In the development of biomaterials, it is critical to choose a type of polymer that responds to a specific temperature. Even an inaccuracy of 1°C can make a big difference," says Ebara.

Performance based on nanoarchitectonics

Since this polymer responds to an ideal temperature in terms of medical application, its practical use in various aspects of regenerative medicine has already been studied. Ebara carried out very precise molecular design and synthesized polymers based on the design.

"This is the fundamental idea behind the International Center for Materials Nanoarchitectonics (MANA) to which I belong. The idea of nanoarchitectonics, as the name indicates, is to design, construct and control molecules at the nano-level. That is the greatest experience I gained from NIMS," says Ebara.

For example, when you construct a building, you accurately estimate its framework structure, as well as the number, widths and lengths of structural columns in your design. Similarly, the desired performance of molecules can be attained only through designing the framework and column structures, and synthesizing them at a nano-size level. However, nano-engineering is not a straightforward business.

"Each of the nanofibers I have developed has a jungle-gym-like structure which contains anticancer drugs and magnetic particles, so to speak. To allow the right amount of anticancer drugs to seep out at 43°C, I carefully designed the molecular structure through detailed calculation for the number of columns to be used in the jungle gym and the heights of the columns and space between them," explains Ebara.

Furthermore, even after the synthesis, Ebara meticulously checked the quality of the structure by carrying out frequent physical property evaluations. If the structure created turned out to be different from the blueprint, he once again reexamined, synthesized and analyzed the structure. By repeating these steps, Ebara gradually attained desirable performance.

Collaboration between medicine and engineering

Ebara feels his collaboration with medical doctor Lee very fortunate. "He understands our perspective as engineers." Ebara also expressed the importance of medicine-engineering collaboration, saying, "If engineers work alone, they tend to focus all their efforts on improving the performance of materials they develop." Dr. Lee's cooperation is critical to conducting mouse experiments. He also gives me his candid advice, such as the convenience of the material from the viewpoint of surgeons working at clinical sites. Through collaboration between Ebara and Lee, R&D of nanofiber materials was greatly advanced to the point where the practical use of the material is now in sight.

Ebara and Dr. Lee met about eight years ago. Ever since he was a student, Ebara had conducted R&D on polymer materials with specific functions called "smart polymers" and explored their applicability to the medical field. In 2007, he was hired at the Medical Center for Translational and Clinical Research where Dr. Lee was working, and gained firsthand knowledge on clinical studies. Through this experience, Ebara decided to seek a career in R&D of smart polymers and joined NIMS that is regarded as a world-class materials research institute in 2009. His first project at NIMS was the development of nanofiber sheets. And in order to achieve practical application of the material as soon as possible, he asked Dr. Lee to work with him.

As a surgeon, Dr. Lee frequently performs surgery to remove cancer cells. After cancer cells are removed, however, they are often found recurring or spreading. To prevent these events, a sort of adjuvant therapy needs to be applied in addition to surgery. Dr. Lee felt that the nanofiber sheets Ebara had developed was a very promising mean of adjuvant therapy, and willingly agreed to collaborate.

Dr. Lee thought at that time, "First, the material was very appealing to me for its capability to provide chemotherapy and thermotherapy at the same time. In addition, I felt that the material is very practical as its generation of heat can be freely turned on and off from outside. By controlling its generation of heat, the timing and amount of anticancer drugs to be released can also be controlled."

Ebara speaks enthusiastically of his goal, "With close collaboration with Dr. Lee, I plan to begin clinical studies on this material in five years and realize its practical use at an early time."

What motivates Ebara to take on this very ambitious challenge? "People should have equal right to receive medical treatments when dealing with life-threatening situations. Across medically underserved areas worldwide, I hope to contribute to closing the gap of medical disparity and saving the lives of as many people as possible by popularizing nanofiber meshes that can be simply attached to target areas." Ebara has an underlying desire to develop an all-in-one medical material that can help people in need of medical attention in regions such as developing countries and disaster affected areas where expensive medicine and sophisticated medical equipment are unavailable.

The development of this material cannot be achieved by Ebara's effort alone. Dr. Lee, student assistants and other NIMS researchers all need to work together to accomplish the goal.

A nanofiber sheet Ebara developed. It looks like ordinary nonwoven fabric, but it contains anticancer drugs and magnetic particles.

Treating pulmonary diseases using marine resources

In efforts to create materials that are used to seal holes in expanding and contracting organs such as lungs and blood vessels, Tetsushi Taguchi at NIMS developed a medical adhesive with high bonding strength, elasticity and biodegradability.

Tetsushi Taguchi
MANA Scientist,
Biomaterials Unit

Yukio Sato
Professor,
Department of Thoracic Surgery,
Faculty of Medicine,
Tsukuba University

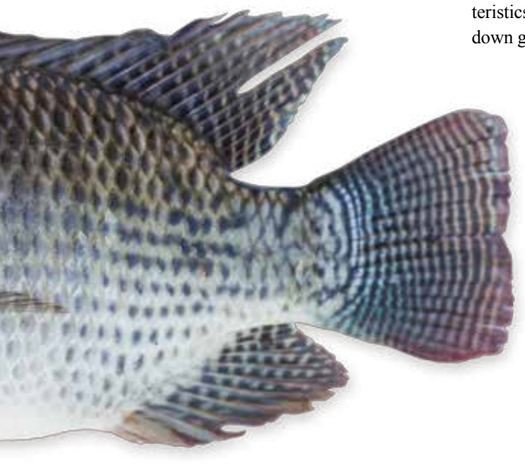
Replacing "fibrin adhesive"

In recent years, patients with pulmonary emphysema have been increasing, especially among middle-aged and older males. The main causes of the disease are aging and excessive smoking. Also of concern is the effect of air pollution caused by such factors as PM2.5 (fine particulate matter).

Emphysema makes lungs brittle, and in severe cases, holes appear in lung tissue, causing air leakage. Even if these holes are sutured, there is still a problem of air leak through the suture holes.

Consequently, adhesives are currently used to seal holes. The existing fibrin adhesive, which takes advantage of blood coagulation reaction, is typically used. Fibrin is produced by combining a type of glycoprotein in blood plasma called fibrinogen and a blood coagulation factor called thrombin. When it coagulates, it acts as an adhesive. Being a blood product, fibrin has advantages of being biocompatible. On the other hand, the fibrin adhesive also has some disadvantages. First, due to its poor bonding strength and elasticity, the adhesive peels off easily after application. In addition, it is expensive and has the risk of being contaminated with hepatitis C virus and other pathogenic factors. Thus, it had been hoped for many years that new adhesives will be developed to replace the fibrin adhesive. Tetsushi Taguchi at NIMS took on the challenge of meeting these needs and successfully developed a new adhesive in 2011.

Taguchi spent about 10 years developing this adhesive. It consists of gelatin derived from cold-water fish and polyethylene glycol–based polymer. Both ingredients are nontoxic to humans and biocompatible, and the resulting adhesive product is nearly 12 times more pressure resistant than the fibrin adhesive. Furthermore, it has extremely high bonding strength and elasticity. Taguchi says, "Because of these characteristics, this adhesive may be applied to any organ. Its use is especially ideal for lungs, which expand and contract vigorously with breathing." It also has the desirable characteristics of being biodegradable and breaking down gradually after surgery.



Great idea: "making gelatin hydrophobic"

The primary reason for this adhesive's high bonding strength and elasticity is that it contains hydrophobic gelatin. The steps involved in the modification of gelatin with hydrophobic groups are as follows.

First, in a solution, replace some of the gelatin's hydrophilic functional groups, such as amino groups and carboxyl groups, with hydrophobic groups. Then, during the surgery, spray the solution on the surface of a target organ while adding a polyethylene glycol-based polymer to the solution. This makes the solution harden on the surface of the organ as the gelatin is cross-linked by polyethylene glycol-based polymer. During this process, some of the hydrophobic groups penetrate through biological tissue, holding the adhesive layer in place like a ship being anchored, so to speak. As a result, the adhesive's bonding strength increases.↙

At the same time, the remaining hydrophobic groups aggregate in a self-organized manner and link together. A loose aggregation is maintained by weak intermolecular interaction. Consequently, as the organ expands and contracts, the aggregated hydrophobic groups also expand and contract in synchrony with the movement of the organ, demonstrating the elastic nature of the adhesive (Figure 1).

For the adhesive to work effectively, an appropriate amount of hydrophobic groups must be applied to the organ. If too many of them are applied, they self-assemble and do not provide an anchor-like function, weakening the adhesive's bonding strength.

"Finding the right ratio of hydrophobic groups in the adhesive was one of the issues I faced in this research," says Taguchi. He has found that a hydrophobic modification ratio of about 10% achieves the best balance between bonding strength and elasticity.

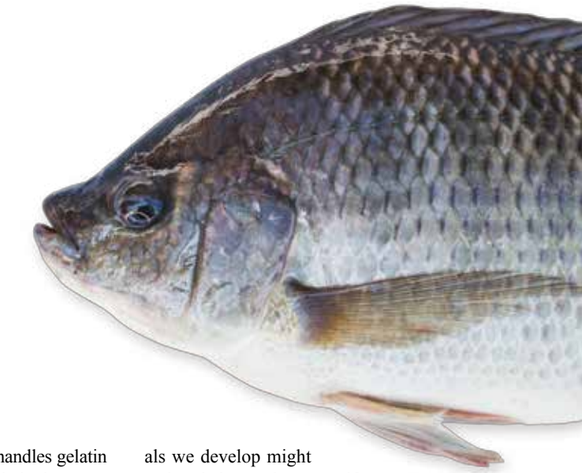
Taguchi had previously learned that hydrophobic polymers adhere well to cell surfaces. This experience provided a hint to him in this current research that the bonding strength of the adhesive may be improved through the modification of gelatin with hydrophobic groups.

"This idea was the biggest reason for the success in the development of this adhesive. But to be honest, I didn't expect that this approach would increase the elasticity of the adhesive. That was a pleasant surprise," says Taguchi looking back on the early days of this study.

Gelatin from fish is better than that from pigs! Solidification temperature is key to successful practical use. ↙

Another key move that brought success to the development of this adhesive is the use of gelatin derived from cold-water fish.

Initially, Taguchi used pig-derived gelatin in his material development. However, given that the phase transition temperature of pig's gelatin, from solid to liquid, is as high as 36.5°C, the gelatin is in a jelly-like solid phase at room temperature. Consequently, when it is used for surgery, it needs to be liquefied beforehand by heating. This requirement is inconvenient for surgery as it needs to be performed as quickly as possible. To deal with this issue, Taguchi consulted with a company that handles gelatin and asked if there is a type of gelatin that stays liquid at room temperature. In the end, he found that such gelatin can be obtained from cold-water fish.



Since the phase transition temperature of gelatin extracted from cold-water fish is as low as about 13.8°C, the gelatin is in the liquid phase at room temperature. As a result, it does not have to be preheated before the surgery, and can be immediately mixed with a crosslinking agent and sprayed during the surgery. Moreover, the cold-fish gelatin is less expensive than mammalian gelatin. So, in consideration of every aspect, cold-fish gelatin is a more suited material for practical use.

With the goal of achieving practical use of the medical adhesive as soon as possible, Taguchi has been in medicine-engineering collaboration with Professor Sato at the Department of Thoracic Surgery, Faculty of Medicine, Tsukuba University, since 2013.

In this joint development effort, Professor Sato applied this adhesive to close a pleural defect formed in the lungs extracted from a pig, and was surprised by its high bonding strength and elasticity.

Professor Sato says, "I felt that this adhesive would be useful not only in treating lungs that expand and contract intensively but also in surgical operations on any other organ systems such as the cardiovascular system and digestive system." Of course, the adhesive requires further improvement toward practical use, and the only way to achieve that is through collaboration between the medical and engineering fields. Regarding the importance of such collaboration, Taguchi says, "Many of us, biomaterials scientists, hope to contribute to medical advancement by developing materials that impress medical workers. However, if we do not have a good understanding of the practical issues medical workers are facing, the materials we develop might end up being useless even if they use cutting-edge technology. To avoid such wasteful and inefficient efforts, it is vital for us to hear opinions from on-site medical workers and develop truly useful materials based on their input."

Professor Sato also says, "I totally agree with Dr. Taguchi. As I practice medicine daily, I often wish that improvements would be made to certain materials. In this regard, we are very fortunate to have NIMS, a world-class materials research institute, in our vicinity in the Tsukuba area for collaborative efforts.

Also, in view of the current situation where most medical equipment is manufactured in Europe and the United States, I hope that Japan will develop superb products at least in the area of biomaterials, taking advantage of its technological strength, and commercialize them in the world market."

Taguchi and Professor Sato are aiming to carry out clinical studies in five years. Taguchi will continue to make efforts in identifying real needs at medical sites, and developing materials to address these needs.

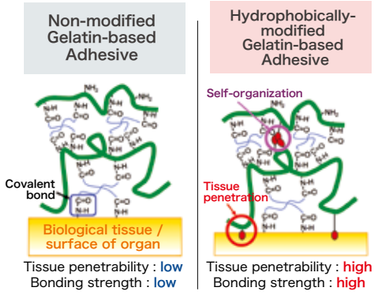


Fig. 1. Difference in adhesiveness due to presence/absence of hydrophobic groups.

Topics

Materials for next-generation medical technologies

Kohsaku Kawakami
MANA Scientist,
Smart Biomaterials Group,
Biomaterials Unit

Development of ultimately safe DDS carrier

Improving drug treatment from the perspective of materials research

Drug delivery systems (DDS) that are used to transport the minimum required quantities of drugs to a target location at the right timing is a promising medical technology. To alleviate patients' pain and discomfort associated with drug treatment, Kohsaku Kawakami at NIMS has been developing DDS materials.

Many drug treatments impose a heavy burden on patients, as seen in anti-cancer therapy that often causes severe side effects and insulin injections that have to be self-administered by diabetics. Kawakami is attempting to solve the issues related to friendliness to patients by developing new materials. In particular, he is focusing many efforts on the development of materials to be used as a "drug carrier" in DDS.

One such example is a drug carrier consisting exclusively of a biological component, which was released to the press in March 2015. This particulate carrier has a diameter of 5 to 20 μm, and in its interior, there are countless minute pores of 2 to 50 nanometers called mesopores. The carrier is capable of holding drugs and efficiently delivering them. While mesoporous particles had been created in the past using such materials as silica and carbon, their safety in human bodies was of concern due to their extensive stability. In contrast, the mesoporous particles Kawakami developed are very safe as they are composed entirely of phospholipids, a biological component. Since phospholipids have already been in use as additives to commercially-available medical products, commercialization of the mesoporous particles is likely to be easy.

Furthermore, since the particles have very low density and can be used as a powder without dispersing them in a liquid, it is feasible to use them, for example, as a powder formulation for pulmonary administration. Another patient-friendly drug carrier comprised of phospholipids, liposomes, has already been commercialized, but it is effective only as a liquid form and therefore its route of administration is almost limited to injection.

"In recent years, the market for biopharmaceuticals has been growing. However, most products are injections as they consist of large molecules that are nearly non-absorbable through oral administration. Consequently, it is hoped that some drugs can be administered through the lungs, which efficiently absorb drugs due to their large surface areas and dense capillaries. The recently developed mesoporous particles are highly safe and can be used as a powder inhalant. So, by using them as a carrier for biopharmaceuticals and applying them through the lungs, it is expected that patients' pain and discomfort associated with drug treatment will be eased," says Kawakami. In general, expectations are growing to realize pulmonary administration of biopharmaceuticals. For example, pulmonary administration of insulin, which cannot be administered orally, reduces the burden on patients.

Kawakami's experience in working at pharmaceutical companies has contributed to the approach he took in this study. "At pharmaceutical companies, I worked to commercialize drugs for about 13 years. That is when I started thinking that I want to ease as much as possible the pain and discomfort that patients feel on a daily basis due to drug treatment." To put this idea into practice, Kawakami joined NIMS, thinking that the development of new materials is critical.

Moreover, Kawakami added, "The mesoporous particles we developed are easy to create, so, their industrialized production can be easily achieved. That is a vital asset." Kawakami's insight into practical application of the product is attributed to his long industry experience in commercialization of products. The mesoporous particles can be created simply by dissolving phospholipids in an organic solvent and freeze-drying it. Furthermore, drugs can be easily added to and integrated into the particles during the freeze-drying step. And by adding or not adding water to the organic solvent, one can create drug carriers that are capable of delivering drugs with various physical properties such as hydrophilic and hydrophobic drugs.

As expectations are rising for the application of this material as DDS carriers, Kawakami is aiming at early commercialization of the product by seeking collaboration with a pharmaceutical company. "I will continue to do my best in reducing patients' pain and discomfort associated with drug treatment by developing NIMS original materials while using my experience in working at pharmaceutical companies."

Controlling the dissolution of magnesium

Toward the realization of bioabsorbable bone plates

Titanium alloy is used for bone fixation devices. However, this option is imposing a heavy burden on patients as it requires a second surgery to remove the plates after the broken bone is healed. Sachiko Hiromoto at NIMS has been studying "bioabsorbable metallic materials" that do not have to be taken out after bonehealing.

A broken bone is fixed with medical devices called "bone plates" until the bone is healed. Currently, titanium alloy, which has high corrosion resistance and strength, is usually used in bone plates.

On the other hand, expectations are high for the commercialization of bone plates that dissolve and disappear in the body. It is because, for example, if titanium-based plates are used to fix broken facial bones, a second surgery is required to take them out, which may leave additional scars on the face and provoke psychological pain. There are also bone plates made of polylactic acid, but the disadvantages of low strength limits practicality.

In her research, Sachiko Hiromoto at NIMS has been aiming at practical use of "bioabsorbable metallic materials" that have sufficient strength and are capable of dissolving in the body after a broken bone is healed, eliminating the need to take out the plates. In 2008, Hiromoto successfully developed a metallic material made of magnesium alloy that is coated with "hydroxyapatite," a main component of bones.

Hiromoto says, "Magnesium is an essential element for the human body and is the fourth most abundant element in the body. While magnesium alloy is not as strong as titanium alloy, it is light, its elastic modulus is comparable to that of bones which enables to properly share the load with bone. Because of these advantageous characteristics, magnesium alloy would be extremely useful for many medical devices used in arms and jaws."

Magnesium alloy had been a promising material for bioabsorbable bone plates. However, the conventional magnesium alloy dissolves too rapidly in the body, as it reacts with water, generating hydrogen gas and hydroxide ions. To achieve practical use of the material, many researchers have been taking an approach of coating it with a material that is more resistant to dissolution in the body. Especially, a hydroxyapatite coating was found suitable as it is highly compatible with bones and is gradually absorbed by them. Thus, ideal treatment of broken bones can be achieved with this material as bone plates made of it disappear when bones are just about to become completely healed. Another advantage of this coating material is that a coating can be formed in an aqueous solution, which can be applied to base material with various shapes and allows for reducing the production cost.

"But it had been generally believed to be impossible to form a hydroxyapatite coating on magnesium alloy in an aqueous solution," says Hiromoto. That is because magnesium alloy immersed in a surface treatment solution releases magnesium ions, which in turn reacts with calcium phosphate, a precursor of hydroxyapatite. This reaction prevents the intended conversion of calcium phosphate into hydroxyapatite.

To solve this problem, Hiromoto came up with the idea that "increasing the concentration of calcium ions in the solution may ensure the production of hydroxyapatite even in the presence of magnesium ions."

After trial and error, Hiromoto came up with a system in which she immersed magnesium alloy into a solution consisting of calcium-ethylenediaminetetraacetic acid, a metal complex, and phosphate. As a result, she successfully coated magnesium alloy with hydroxyapatite.

Hiromoto then conducted implantation test using mice into which hydroxyapatite-coated or uncoated magnesium alloys were subcutaneously implanted for 16 weeks. In this study, she found that in mice with an uncoated alloy implanted, magnesium alloy dissolved and produced hydrogen gas in their bodies, causing skin to swell and inflammation in the surrounding tissues. In contrast, in mice with a coated alloy implanted, no such events were observed.

"I was able to achieve the goal of coating magnesium alloy with hydroxyapatite in an aqueous solution, which was generally said to be impossible. While the initial strength of the material can be maintained for a while with the developed coating, to achieve its practical use as bone plates, it is still necessary to realize dissolution of the material in synchrony with the healing of a broken bone. In efforts toward commercialization of the material, I would like to collaborate with other NIMS divisions and other organizations." says Hiromoto.

Sachiko Hiromoto
MANA Scientist,
Smart Biomaterials Group,
Biomaterials Unit

Topics
Materials for next-generation medical technologies

Controlling Cell Proliferation Based on the Different Valence States of Metal Elements

Focus on the "Ce valence states" of cerium oxide

The goal of tissue engineering is to develop artificial tissues and organs. Development and improvement of scaffold materials in tissue engineering play a role in promoting cell growth and proliferation. The ability of biodegradable polymer matrix mixed with cerium oxide nanoparticles, serving as a scaffold material, to promote proliferation of adherent cells has been reported. The mechanism behind this phenomenon, however, is still unclear. Tamaki Naganuma, MANA Scientist, has been attempting to elucidate the interaction mechanism between cerium oxide and cell proliferation behavior, and also to find out novel factors for controlling cell proliferation.

Cerium oxide is a type of ceramic material, and has been mainly investigated in various fields for fuel cell, exhaust catalyst and oxygen storage materials. Recently, research into cerium oxide materials has been pursued toward therapeutic applications in a biomedical field. This is due to a relatively low toxicity among metal oxides and an enzyme-mimic capability to scavenge reactive oxygen species that are linked to cancer and diabetes.

In addition to its therapeutic applications, Tamaki Naganuma et al. proposed the use of cerium oxide nanoparticles for tissue engineering applications: "surface functionalization" of scaffold materials. Surface functionalization is a method to modify material surfaces by adding functional groups and molecules. Since adherent cells attach to scaffold surfaces, surface functionalization of scaffolds is essential in terms of enhancing cell growth and proliferation.

The ability of biodegradable polymer matrix mixed with cerium oxide nanoparticles, serving as a scaffold material, to promote proliferation of adherent cells has been reported. It was, however, unclear whether cerium oxide itself in scaffold materials promotes cell proliferation or altered surface morphologies / characteristics of polymer scaffold materials caused by added cerium oxide nanoparticles.

Naganuma focused on valence states of Cerium (Ce), and designed the following new surface functionalization of polymer scaffolds to identify whether Ce valence states relate to cell proliferation.

First, to investigate an interaction between adherent cells and cerium oxide, the surface of the biodegradable polymer was covered with cerium oxide nanoparticle layers. Subsequently, regions of highly concentrated trivalent and tetravalent Ce were created on the cerium oxide nanoparticle layers side by side (Figure 1).

"The formation of stable and highly concentrated trivalent Ce in cerium oxide nanoparticles was a key to success in this step," says Naganuma. Generally, cerium oxide has the mixed valence states of trivalent and tetravalent Ce, but is occupied with tetravalent Ce (the ratio of about 20 % trivalent to 80 % tetravalent) due to the tendency of trivalent Ce to easily oxidize and convert to the tetravalent state in air.

To address this issue, Naganuma formed very thin nanoparticle layers — up to approximately 20 nanometers thick — on the polymer surfaces, and then induced oxygen vacancies in the nanoparticles by argon ion irradiation. As a result, she succeeded in the formation of stable and highly concentrated trivalent Ce in cerium oxide nanoparticles. The use of this material made it possible, for the first time, to investigate the effect of Ce valence states of cerium oxide nanoparticles on cell proliferation.

When cells were cultured on this material, those that adhered to the tetravalent Ce region rapidly proliferated. In contrast, the proliferation of cells that adhered to the trivalent Ce region was surprisingly inhibited (Figure 2).

"These findings revealed that different Ce valence states of cerium oxide promoted or inhibited cell proliferation. This indicates that valence states of metal elements could be a novel extracellular factor influencing cell proliferation," says Naganuma.

It is even conceivable that different valence states of other metal elements existing in vivo may replicate this phenomenon. In fact, it may be feasible to control cell proliferation from outside of cells by applying different valence states of metal elements.

"In the future, we will address elucidation of the mechanism by which different Ce valence states influence cell proliferation. Through this approach to elucidating the mechanism, we may gain insight applicable not only to promoting the proliferation of normal cells, but also to inhibiting the proliferation of cancer cells," says Naganuma.

The prospective study based on these findings will be anticipated in order to yield innovative biomaterials under a medicine-engineering collaboration.

Fig. 1. Formation of cerium oxide nanoparticle layers and highly concentrated Ce^{3+}/Ce^{4+} regions on the surface of biodegradable polymer (cross-sectional diagram).

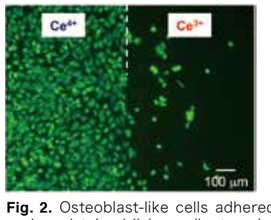


Fig. 2. Osteoblast-like cells adhered to the Ce^{3+}/Ce^{4+} regions (stained living cells, top-viewing observation). Cell proliferation behavior on Ce^{3+}/Ce^{4+} regions was clearly different. (*Biomaterials* 2014, **35**, 4441−4453.)

Tamaki Naganuma
MANA Scientist, Smart Biomaterials Group, Biomaterials Unit

Sciense is even more amazing than you think (maybe...) 6

Learning about manufacturing from the growth of living things

Written by Akio Etori
Title lettering and illustration by Shinsuke Yoshitake

There are various products that support comfortable and lively living. They include cars, electronic products, watches, cameras, medical products, houses, and so on. These products are in their top condition when they are just manufactured, in terms of their functions and qualities. In other words, these products provide top-notch performance when they are brand new but their performance gradually deteriorates with time.

On the other hand, organisms are different from these man-made products. Any living thing, of course, is destined to age and eventually die, like any artificial product is subject to deterioration and end-of-life. The difference between the two is that for organisms, their prime does not come at birth. For example, higher organisms are weak and nearly helpless at birth. Their physical shape peaks after they take in nutrients, grow and reach maturity.

Why do these differences exist between artificial products and organisms, nature's creation?

One key reason is that they are made of different "materials."

Ancient humans made things out of naturally-occurring materials such as earth, rocks and wood. As civilization progressed, humans began using refined metals such as iron and copper. And more recently, they started using artificial materials such as plastics.

These materials need to be adjusted in size and shape depending on what they are used for. So, a large amount is typically prepared to begin with, for example, in the form of large mass, wide plate or long tube, and then it is cut into pieces of appropriate sizes. Since the products we use have specific shapes and weights, and since it is desirable for them to be long-lasting, the materials used to create them need to have proper hardness and durability. Thus, one premise for manufacturing goods is that the component materials themselves maintain their physical properties over time.

In contrast, what are bodies of organisms such as humans made of? The cell is the basic unit of life. Fertilization triggers a single cell (e.g., an egg cell in humans) to divide into two cells, then four, and so on. This process eventually forms a fully-functional human body. Genes play a central role in synthesizing proteins that are a major component of cells. A gene is a segment of deoxyribonucleic acid (DNA) that includes of four types of nucleobases (adenine, cytosine, guanine and thymine), and the order of these bases determines the types of proteins to be synthesized.

It is said that a typical human adult body is made up of about 60 trillion cells, in which dead cells are constantly replaced with new cells.

All parts of a living body are created with extraordinary precision based on a program determined by genes. The longevity of cells, the building blocks of organisms, is so short that they need to be replaced frequently in various body parts. This is how organisms use "materials."

If a sponge, a primitive animal, is cut into pieces and placed in a solution, it is capable of reforming its body, although higher animals such as humans have no such capability due to their very complex body structures.

The approach to manufacturing conventional physical products may be viewed as top-down in the sense that a large material is reduced to a proper size and shape by such means as cutting and shaving. Conversely, the approach involved in the growth of organisms may be perceived as bottom-up in the sense that a living body grows through synthesis and integration of small particles (proteins) based on a program.

Actually, nanotechnology is a tool that we can use to perform a bottom-up approach, given hints by the growth of organisms, in manufacturing various products. In the future, scientists may master this approach and apply it to the development of beneficial medical technology.

Akio Etori: Born in 1934. Science journalist. After graduating from College of Arts and Sciences, the University of Tokyo, he produced mainly science programs as a television producer and director at Nihon Educational Television (current TV Asahi) and TV Tokyo, after which he became the editor in chief of the science magazine Nikkei Science. Successively he held posts including director of Nikkei Science Inc., executive director of Mita Press Inc., visiting professor of the Research Center for Advanced Science and Technology, the University of Tokyo, and director of the Japan Science Foundation.

NIMS NEWS

1 NIMS Concludes a MOU with DGRSDT of Algeria

(March 30th, 2015) President Prof. Sukekatsu Ushioda of NIMS signed a Memorandum of Understanding (MOU) with the Directorate General for Scientific Research and Technology Development (DGRSDT) of the People's Democratic Republic of Algeria. H.E. Mr. Mohamed El Amine Bencherif, new Ambassador Extraordinary and Plenipotentiary to Japan who just took office at the end of last February, witnessed the signing. His presence reinforces importance of this MOU and the research collaboration between the two institutions.

DGRSDT is one of the bureaus in the Ministry of Higher Education and Scientific Research (MESRS) and responsible for the scientific research of entire Algeria, in particular programming and evaluating the scientific research, developing the human resources, supporting scientific cooperation, financing university research, etc. It also directly operates eleven national laboratories including those for sustainable energy and biotechnology.

Based on the new MOU, DGRSDT will be coordinating the collaboration between NIMS and the many universities and national laboratories in Algeria, and a more active future cooperation can be envisaged between NIMS and academic institutions in Algeria.

(left to right): Prof. Hacène Belbachir, Director of Research Programming, Evaluation and Prospective, DGRSDT, and Prof. Sukekatsu Ushioda, President of NIMS.

2 First Publication of about 1,000 Materials Studied for Superconductivity including "Negative Cases"

(May 18, 2015) NIMS Vice President Eiji Muromachi, NIMS Invited Researcher Hiroaki Kumakura and researchers led by Hideo Hosono, Professor of Tokyo Institute of Technology, published their joint study on a wide variety of superconducting and non-superconducting materials in Science and Technology of Advanced Materials (STAM), an open access journal issued and supported by NIMS.

Because ordinary research papers report only "positive cases" without sharing information on non-superconducting materials, there is a chance that other researchers may repeat studies on the same non-superconducting materials. However, 1,000 materials are listed in this review paper including newly discovered superconducting materials as well as about 700 non-superconducting materials.

"This is probably the first paper to list non-superconducting materials tested. I believe this paper will provide valuable data to superconductivity researchers," says Professor Hosono, the first author of the above-mentioned paper. Based on the wish of the research team to promote superconductivity research without wasting efforts worldwide, the team published the study in the open access journal STAM. This research compiled study results yielded over four years under the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST).

Related link
*"Exploration of new superconductors and functional materials, and fabrication of superconducting tapes and wires of iron pnictides" Hideo Hosono, Keiichi Tanabe, Eiji Muromachi, Hiroshi Kageyama, Shoji Yamanaka, Hiroaki Kumakura, Minoru Nohara, Hidenori Hiramatsu and Satoru Fujitsu. Sci. Technol. Adv. Mater. Vol. 16 (2015) p. 033503 (http://dx.doi.org/10.1088/1468-6996/16/3/033503)

Vice President Eiji Muromachi　　Prof. Hideo Hosono

Hello from NIMS

Two years ago, when I decided to join NIMS as a JSPS post-doctoral fellow after my Ph. D. in Strasbourg, I faced a much unexpected question: why Japan? Since I came from an international background allowing me to live in different western countries, that choice was obvious to me: Japan because I had no knowledge about it, its culture nor its language. That was a winning bet. NIMS offers an exceptional concentration of characterization facilities and I could enjoy a good level of independence in the team of my host. Joining ICYS recently brought everything up to a next exciting level as well as providing a real luxury: time for deeply learning and investigating my topics. Outside of the lab, I was quickly seduced by Japan and its finely shaded society while visiting the main touristic spots or better understanding the culture with Japanese friends. As an alumni from Strasbourg used to describe his favorite land: Kennst du das Land, wo die Zitronen blühn ? (Goethe, "Do you know the land where lemons blossom?). What if it were Japan ?

Practicing non-verbal communication in Nara.

Rydzek Gaulthier (French)
May 2013-present
JSPS(Team of Prof.Ariga)
From 2015: ICYS-MANA

NIMS NOW International 2015. Vol.13 No.3
National Institute for Materials Science
http://www.nims.go.jp/eng/publicity/nimsnow/

photo by Michito Ishikawa　text by Kumi Yamada　editorial design by Iala Salon Associates

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